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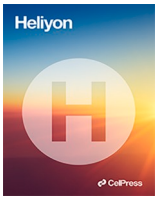

Research article

# Comparison of clopidogrel and ticagrelor in treating acute coronary syndrome undergoing PCI: A systematic review and meta-analysis

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ABSTRACT

*Objective:* The study aims to evaluate and compare the efficacy and safety between ticagrelor and clopidogrel in acute coronary syndrome (ACS) patients undergoing percutaneous coronary intervention (PCI).

*Methods:* We searched MEDLINE (via PubMed), Cochrane, Embase, and the Cochrane library databases for eligible citations (the last search was up to December 2021). Subgroup analyses were performed based on region, study design, dose, and single-center/multicenter. Meta regressions were conducted to explore the source of heterogeneity. A sensitivity analysis was conducted to assess the robustness of the results. Funnel plots and Egger's test were preformed to test publication bias of the meta-analysis.

*Results:* A total of 29 studies were included, totaling 165,981 patients. Ticagrelor reduced the overall incidence rate of major adverse cardiovascular events (MACEs) (HR 0.74; 95% CI, 0.62, 0.89; P = 0.001; $I^2$ = 88.3%, P < 0.001) and all-cause mortality (HR 0.85; 95% CI, 0.75, 0.97; P = 0.019; $I^2$ = 39.7%, P = 0.052) compared with clopidogrel. However, there was a higher risk of major bleeding (HR 1.21; 95% CI, 1.02,1.44; P = 0.026, $I^2$ = 59.3%, P = 0.012) and all bleeding (HR 1.42; 95% CI, 1.24, 1.62; P < 0.001, $I^2$ = 76.4%, P < 0.001) with ticagrelor compared to clopidogrel. The stability of the results was demonstrated by sensitivity analysis. Furthermore, subgroup analyses and meta-regression revealed that the heterogeneity in the study may stem from factors such as whether it was conducted in a single-center or multicenter setting, as well as the geographical region.

*Conclusion:* Ticagrelor has demonstrated superior efficacy compared to clopidogrel in ACS patients undergoing PCI, particularly in Asia and Europe. Nevertheless, it is crucial to acknowledge

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that the utilization of ticagrelor is linked to a heightened risk of bleeding. To provide guidance for clinical decision-making regarding the use of ticagrelor, future multicenter randomized trials that are relevant and encompass longer follow-up periods are necessary.
*The category of the manuscript: a meta-analysis:* PROSPERO registration number CRD42021274198.

## 1. Introduction

Acute coronary syndrome (ACS) is a series of clinical syndromes which is based on pathological basis of coronary atherosclerotic plaque rupture or erosion and occlusive thrombosis. And ACS is a mortality in the United States with an annual incidence of approximately 1 million [1]. Patients with ACS, especially acute myocardial infarction (AMI), have a higher risk of mortality and severe complications, including arrhythmia, bradycardia, and heart failure [2]. Based on the 2018 European Society of Cardiology (ESC) and European Association for Cardiothoracic Surgery (EACTS) guidelines, percutaneous coronary intervention (PCI) is strongly recommended as a class I treatment for cardiovascular diseases in high-risk ACS patients [3,4]. Besides, dual antiplatelet therapy (DAPT) refers to the combination of aspirin and a purinergic receptor type Y, subtype 12 (P2Y12) inhibitor (clopidogrel, prasugrel, or ticagrelor) have been recommended for a minimum duration of 12 months in ACS patients [5] to prevent stent thrombosis following PCI with drug-eluting stents (DES) [6].

Ticagrelor, which does not require metabolic activation, has a strong antiplatelet effect and little individual difference, which provides faster and more significant inhibiting effects against platelet aggregation than clopidogrel [7]. Despite ticagrelor being widely used in ACS patients, the Platelet Inhibition and Patient Outcomes (PLATO) trial demonstrated its efficacy in reducing the risk of myocardial infarction (MI), stroke, and death from vascular causes [8]. However, two large randomized controlled trials (RCTs) [9,10] and observational trials [11,12] revealed no significant advantages of ticagrelor in reducing ischemic events in ACS patients.

Previous meta-analyses [13,14] have compared the effect of ticagrelor and clopidogrel on patients with ACS who underwent PCI. However, these studies did not consider important factors such as dosage, geographical region, and whether the study was conducted at a single center or multiple centers, which may influence the effects of these medications. Furthermore, since the publication of the previous review, a total of 18 new studies involving 131,566 patients [15–23], which assessed the effect of ticagrelor and clopidogrel on ACS patients undergoing PCI, have been published [15–33]. Given the aforementioned factors, we preferred this comprehensive systematic review and meta-analysis to compare the efficacy and safety between ticagrelor and clopidogrel in ACS patients who underwent PCI. Additionally, we aimed to explore the potential source of heterogeneity through subgroup analyses based on geographical region, dosage, single-center versus multicenter studies, and the duration of follow-up.

## 2. Methods

We conducted this systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [33]. This study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) with ID CRD42021274198.

### 2.1. Data sources and search strategy

We searched for eligible studies in electronic databases, namely MEDLINE (via PubMed), Embase, and the Cochrane Library. The search was conducted up until December 2021. The complete literature search strategy in each database was provided in Supplementary Appendices 1.

### 2.2. Inclusion and exclusion criteria

We selected the articles based on the following eligibility criteria: (1) all patients were diagnosed with ACS undergoing PCI; (2) the articles compared the efficacy or/and safety between clopidogrel and ticagrelor of DAPT and (3) RCTs, cohort studies and case-control studies were considered. Exclusion criteria were as follows: (1) not presented in English or Chinese; (2) review articles, meta-analyses, or conference abstracts and (3) different studies using the same sample.

### 2.3. Data extraction

Two reviewers independently (JY and YPB) reviewed all relevant and eligible literatures using standardized data-abstraction forms and any disagreements were solved by the third investigator (MZ). Two reviewers independently extracted information from each article encompassing: (1) bibliographic details: the first author, published year, study design; (2) demographic and clinical information: monocenter/multicenter, sample size, the number of male/female, age, country/region, follow-up duration, drop-out and baseline characteristics of patients; (3) the information of ticagrelor and clopidogrel: medication dose and frequency; and (4) prognosis outcome: clinical outcomes and related definition, hazard ratio (HR) and 95% confidence intervals (CI).

### 2.4. Study outcomes

The primary endpoints of this study were the incidence of major adverse cardiovascular events (MACEs) (a composite event of cardiac-mediated death, MI, stent thrombosis, and ischemic stroke), all-cause mortality, MI, stroke, and urgent revascularization. The secondary endpoints were all bleeding and major bleeding which includes the appearance of bleeding academic research consortium (BARC)-defined majoring bleeding (BARC type ≥ three bleeding events), retroperitoneal bleeding, intracranial bleeding, the decline in hemoglobin levels (≥4 g/dL) during hospitalization, transfusion with overt bleeding, and bleeding requiring surgical intervention.

### 2.5. Assessment of study quality

In order to evaluate the quality of the included studies, we utilized the Cochrane risk bias tool and the Newcastle-Ottawa Scale [34, 35]. These tools allowed us to assess the risk of bias and the methodological quality of each study. Two reviewers independently assessed the risk of bias in the non-randomized studies using the Newcastle-Ottawa Scale. The Newcastle–Ottawa Scale was used to assess selection, comparability, exposure, and risk of bias. The Cochrane risk of bias tool [35] for RCT was utilized to evaluate bias in seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias (anything else, ideally prespecified).

### 2.6. Statistical analyses

The whole data statistical analyses were performed through R studio 4.1.3 with loading meta package (version 5.2–0) and STATA 15.0 (Stata Corp, College Station, TX). All endpoints were presented as HR with 95% CI, representing the risk associated with ticagrelor

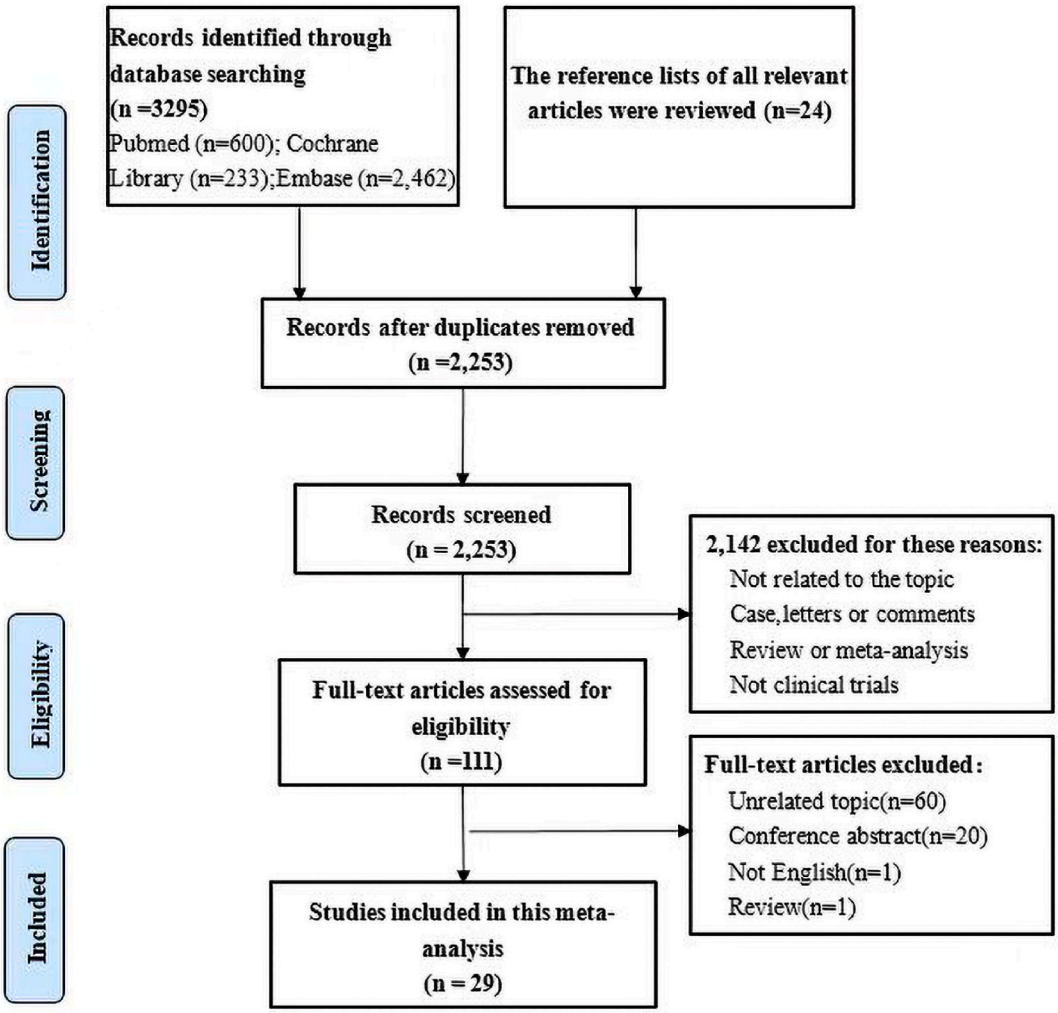


**Fig. 1.** PRISMA flow diagram outlining the literature search process.

**Table 1**
Study characteristics and baseline demographics.

| First author | Year | Study design | S/M | available data (Yes/No) * | Country | Clopidogrel/Ticagrelor | | | | | | | | | Median follow-up, months | Drop-out, % | NOS scores |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Patients, n | Age, years | Male, % | Hypertension, % | Diabetes, % | Dyslipidemia, % | Smoker, % | Dose, mg/day | Initial dose, mg | | | |
| Angiolillo [15] | 2016 | Cohort | M | Yes | Greece | 959/717 | 65.3/60.1 | 78.3/84.9 | 59.1/52.7 | 24.8/21.2 | 45.0/46.9 | 48.2/61.2 | 75/180 | – | 12 | 5.0 | 7 |
| Chen [18] | 2020 | Cohort | M | Yes | Taiwan | 369/241 | 70.7/70.6 | 71.6/72.8 | 77.6/78.1 | 54.7/58.1 | 53.3/49.0 | 25.7/23.8 | 75/180 | – | 12 | 0.0 | 7 |
| Choe [19] | 2019 | Cohort | M | Yes | Korea | 7073/1474 | 67.0/63.0 | 54.3/60.2 | 59.4/65.9 | 40.0/37.1 | 15.0/15.7 | 54.3/60.2 | 75/180 | – | 15 | 5.0 | 6 |
| Nur'Amin [25] | 2017 | Cohort | S | Yes | Indonesia | 250/111 | 55.8/55.9 | 92.8/92.8 | 60.4/58.6 | 41.6/40.5 | 33.4/34.8 | 43.6/36.1 | 75/180 | – | 3.7 | 0.0 | 6 |
| Steg [27] | 2010 | RCT | M | Yes | France | 3792/3752 | 59.0/59.0 | 76.6/75.8 | 58.3/59.3 | 21.5/19.1 | 39.3/39.0 | 44.3/45.9 | 75/180 | – | 9.2 | 18.8 | – |
| Turgeon [28] | 2020 | Cohort | M | Yes | Canada | 7109/4076 | 62.0/60.0 | 75.3/74.2 | 68.3/62.1 | 25.4/23.7 | 58.6/51.3 | 32.4/26.0 | – | – | 12 | 19.5 | 7 |
| Wang [29] | 2018 | Cohort | S | Yes | China | 20,037/779 | 60.9/60.5 | 75.1/71.6 | 54.5/57.9 | 23.8/24.6 | – | 57.8/57.3 | – | – | 12 | – | 5 |
| You [30] | 2020 | Cohort | M | Yes | U.S. | 31,290/31,290 | – | 70.8/70.6 | 72.2/72.5 | 10.4/10.6 | 67.5/68.0 | – | – | – | 12 | 22.6 | 5 |
| Zhao [31] | 2020 | Case-control | M | Yes | China | 8520/2992 | 59.7/61.6 | 79.2/80.3 | 49/47.4 | 19.3/19.9 | 7.0/5.9 | 49.6/53.2 | 75/180 | – | 12 | – | 5 |
| Zheng [32] | 2019 | Cohort | S | Yes | China | 240/240 | 64.1/64.0 | 73.8/74.6 | 58.8/57.1 | 24.6/25.4 | – | 50.0/24.5 | 75/180 | – | 12 | 5.3 | 7 |
| Krishnamurthy [37] | 2019 | Cohort | S | Yes | China | 1648/811 | 65.0/63.0 | 71.5/72.4 | 41.7/39.1 | 14.3/16.4 | 31.8/3.2 | 64.9/62.9 | 75/180 | 600/180 | 12 | 0.1 | 7 |
| Ren [38] | 2016 | Cohort | S | Yes | China | 151/149 | 55.0/56.0 | 70.0/68.0 | – | – | – | – | 75/180 | 300/180 | 12 | – | 5 |
| Tang [39] | 2016 | Cohort | S | Yes | China | 200/200 | 64.2/64.4 | 73.0/71.0 | 58.0/61.0 | 21.0/29.0 | 37.0/44.0 | 62.0/57.0 | 75/180 | 600/180 | 6 | 0.3 | 6 |
| Goto [10] | 2015 | RCT | M | Yes | Japanese, Taiwanese, and South Korean | 400/401 | 66.0/67.0 | 76.7/76.3 | 72.5/76.1 | 38.4/31.8 | 72.3/78.3 | 39.3/37.7 | 75/180 | 300/180 | 12 | 6.2 | – |
| Park [12] | 2016 | Cohort | M | Yes | Korea | 1337/1377 | 62.2/62.3 | 78.9/77.7 | 46.9/46.1 | 22.8/23.7 | 11.3/11.3 | 42.7/42.2 | 75/180 | 300-600/180 | 6 | 29.0 | 6 |
| Alexopoulos [41] | 2016 | Cohort | M | Yes | Greece | 959/717 | 65.3/60.1 | 78.3/84.9 | 59.1/52.7 | 24.8/21.2 | 45.0/46.9 | 45.0/61.2 | 75/180 | – | 12 | 0.1 | 7 |
| Velders [42] | 2016 | RCT | M | Yes | Sydney | 2486/2463 | 59.0/59.0 | 78.1/76.9 | 56.5/57.9 | 19.4/17.3 | 38.9/38.1 | 46.8/49.4 | 75/180 | 300/180 | 12 | 0.0 | – |
| Kim [43] | 2019 | Case-control | M | Yes | Korea | 15,459/4811 | 60.0/57.0 | 81.0/86.0 | 69.0/68.0 | 56.0/55.0 | – | 2.3/1.3 | -/180 | -/180 | 12 | – | 8 |
| HW [44] | 2016 | Case-control | S | Yes | Indonesia | 250/111 | 55.9/55.8 | 92.8/82.8 | 60.4/58.6 | 41.6/40.5 | 33.6/34.2 | 43.6/36.0 | 75/180 | – | 12 | 0.0 | 7 |

(*continued on next page*)

**Table 1** (*continued*)

| First author | Year | Study design | S/M | available data (Yes/No) * | Country | Clopidogrel/Ticagrelor | | | | | | | | | Median follow-up, months | Drop-out, % | NOS scores |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Patients, n | Age, years | Male, % | Hypertension, % | Diabetes, % | Dyslipidemia, % | Smoker, % | Dose, mg/day | Initial dose, mg | | | |
| Choi [46] | 2017 | RCT | S | Yes | South Korea | 22/40 | 65.0/61.0 | 68.0/82.5 | 41.0/57.5 | 18.0/42.5 | 18.0/7.5 | 30.0/42.5 | 75/180 | – | 1 | 0.1 | – |
| Orme [26] | 2018 | NA | S | No | U.S | 57/54 | 64.6/66.9 | 77.0/85.0 | 68.0/69.0 | 21.0/20.0 | 90.0/87.0 | 12.0/11.0 | 75/180 | – | 1 | – | 7 |
| | | | | | | 57/51 | 64.6/66.0 | 77.0/82.0 | 68.0/67.0 | 21.0/24.0 | 90.0/96.0 | 12.0/12.0 | 75/180 | – | 1 | | |
| Angiolillo [16] | 2016 | RCT | M | No | U.S. | – | 63.0/60.1 | 73.5/66.7 | 98.0/86.3 | 32.7/39.2 | 85.9/74.5 | – | 75/180 | – | 0.003 | 8.0 | – |
| Brener [17] | 2019 | Case-control | S | No | U.S. | 774/665 | 66.2/65.9 | 60.0/59.6 | 87.6/85.6 | 51.2/47.2 | 79.7/77.3 | 23.9/25.1 | – | – | 12 | – | 5 |
| Gao [20] | 2018 | RCT | S | No | China | 96/97 | 53.73/55.9 | 42.0/46.0 | 43.8/38.1 | – | – | 55.2/50.2 | 75/180 | 600/180 | 1 | 0.0 | – |
| Jing [22] | 2016 | RCT | S | No | China | 94/94 | 55.0/59.0 | 61.7/57.4 | 54.2/59.6 | 24.5/27.7 | 46.7/38.2 | 38.2/35.1 | 75/180 | 600/180 | 12 | 14.9 | – |
| Jiang [21] | 2018 | Case-control | S | No | China | 125/78 | 61.0/59.0 | 65.5/62.4 | 59.2/69.2 | 22.6/14.1 | – | 40.0/50.0 | 75/180 | – | 12 | 0.0 | 6 |
| Li [23] | 2016 | Case-control | M | No | China | 175/175 | – | – | – | – | – | – | 75/180 | 600/180 | 1 | – | 5 |
| Nct [24] | 2014 | RCT | M | No | U. S. | 49/51 | 63.0/60.1 | 73.5/66.7 | 98.0/86.3 | 32.7/39.2 | 85.7/74.5 | – | 75/180 | 600/180 | 0.011 | 8.0 | – |
| Hee [40] | 2019 | Case-control | S | No | Australia | 232/423 | 64.5/59.5 | 76.3/81.3 | 69.4/54.9 | 37.1/22.8 | 59.6/58.9 | 35.7/49.1 | 75/180 | 600/180 | 32.4 | – | 6 |

RCT, Randomized controlled trial; NOS, Newcastle-Ottawa scale; S/M, Single-center/multicenter; *: available data included in pooled data.

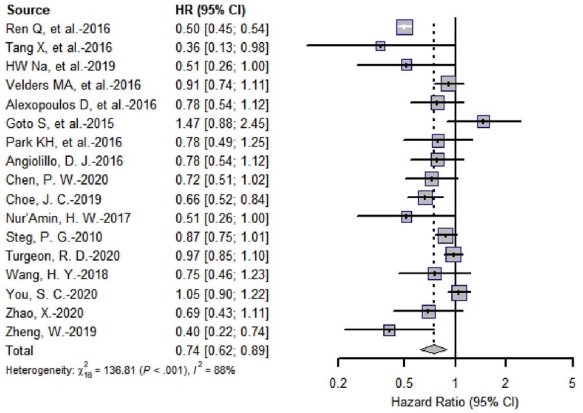


**Fig. 2.** Forest plot of MACE.

relative to clopidogrel. The statistical analyses of the meta-analysis were presented in forest plots. The $I^2$ statistic and *P*-value of Cochrane's Q test were used to assess the heterogeneity of effects, and when the result showed $I^2$>50% or P < 0.05, it demonstrated the studies had severe heterogeneity [36]. We calculated pooled estimates of the HR by using the random-effects model (DerSimonian-Laird method).

Outcomes were stratified by study design, region, dose, single-center/multicenter and follow-up duration to reduce the risk of bias. Several subgroups were also analyzed, including regions divided into Europe, Asia, Oceania, South America, and North America; the study design divided into RCT and non-RCT, and the dose of clopidogrel divided into 300 mg and 75 mg QD, 600 mg and 75 mg QD, 75 mg QD and NA subgroup (means dose of ticagrelor not available), the dose of ticagrelor divided into 180 mg and 90 mg BID, 90 mg BID and NA subgroup (means dose of ticagrelor not available); follow-up duration (≤6months vs. > 6months) and single-center/multicenter. In addition, in these two studies [19,32], cardiac death was regarded as all-cause mortality, and in the other two studies [15,19], non-fatal MI was regarded as MI through integration.

A Chi-square test was performed to assess differences between the subgroups. *P*-value <0.05 was considered statistically significant. In addition, the funnel plot and Egger's test were used to assess publication bias. Finally, sensitivity analysis was performed by omitting each study and calculating the pooled HR and 95%CI of remaining studies through STATA to test the stability of statistical results.

## 3. Results

### 3.1. Study selection and baseline characteristics

A total of 3319 studies were identified, and 2253 abstracts were screened and assessed for potential inclusion in the study. In addition, 111 full-text manuscripts were assessed for eligibility, and 82 of them were excluded as they did not meet the inclusion criteria. Therefore, only 29 studies involving 165,981 patients were included in the study [10,15–32,37–40](Fig. 1). The study characteristics, the main baseline characteristics, dose, follow-up duration and drop-out are shown in Table 1. The mean age was 62.2 years (range 53.7 years–70.7 years). Follow-up durations were range 8 h–32.4 months. And the maintenance dose of clopidogrel was 75 mg once daily, and the maintenance dose of ticagrelor was 90 mg twice daily. And the clinical outcomes are in Supplementary Appendices 3.

### 3.2. Quality assessment

The observational studies included in the analysis were of moderate to high quality, with Newcastle–Ottawa Scale (NOS) scores [41] ranging from 5 to 8 (Supplementary Appendices 4 and 5). The lower NOS scores can be attributed to several reasons outlined below. Firstly, two studies lacked clear definition of control groups and failed to ascertain the exposure accurately [23,31] Additionally, three trials did not provide sufficient information regarding the adequacy of follow-up for the cohorts [17,25,29]. Most of RCTs had a low risk of bias based on the Cochrane risk of bias tool [35] (Supplementary Appendices 6), but two trials [22,24] did not report complete outcome data.

## 4. Primary efficacy outcomes

### 4.1. Major adverse cardiovascular events

A total of 138,012 patients were identified in 17 studies. Ticagrelor was found to be associated with a reduction in the primary

**Table 2**
Subgroup analysis of clinical outcomes.

| Subgroup | No. of studies | No. of patients | Effect value | | Heterogeneity | | | $P_{interaction}$ |
|---|---|---|---|---|---|---|---|---|
| | | | HR (95%CI) | *P*-value | *I* [2]% | Tau [2] | *P*-value | |
| **MACE** | | | | | | | | |
| **Region** | | | | | | | | |
| Europe | 2 | 9583 | 0.86 (0.75,0.98) | 0.028 | 0 | 0.063 | 0.587 | 0.003 |
| North America | 2 | 73,765 | 1.00 (0.91,1.11) | 0.958 | 0 | 0 | 0.436 | |
| Asia | 11 | 48,039 | 0.64 (0.52,0.79) | <0.001 | 66.5 | 0 | 0.001 | |
| Oceania | 1 | 4949 | 0.91 (0.74,1.11) | 0.357 | – | – | – | |
| South America | 1 | 1676 | 0.78 (0.54,1.12) | 0.182 | – | – | – | |
| **Study design** | | | | | | | | |
| RCT | 3 | 13,294 | 0.94 (0.78,1.13) | 0.500 | 46.6 | 0.012 | 0.154 | 0.030 |
| Non-RCT | 14 | 124,718 | 0.68 (0.55,0.85) | 0.001 | 88.7 | 0.124 | <0.001 | |
| **Single-center/multicenter** | | | | | | | | |
| Single-center | 6 | 22,718 | 0.50 (0.46,0.55) | <0.001 | 0 | 0 | 0.629 | <0.001 |
| Multicenter | 11 | 115,294 | 0.87 (0.79,0.97) | 0.012 | 48.4 | 0.013 | 0.036 | |
| **Follow-up duration** | | | | | | | | |
| ≤6 months | 3 | 3414 | 0.55 (0.46,0.77) | <0.001 | 49.5 | 0.219 | 0.138 | 0.031 |
| >6 months | 14 | 134,598 | 0.82 (0.73,0.93) | 0.001 | 58.7 | 0.025 | 0.003 | |
| **Dose of ticagrelor** | | | | | | | | |
| 180 mg and 90 mg BID | 5 | 9164 | 0.75 (0.48,1.16) | 0.194 | 91.2 | <0.001 | <0.001 | <0.001 |
| 90 mg BID | 9 | 34,267 | 0.72 (0.62,0.83) | <0.001 | 30.8 | 0.172 | 0.172 | |
| NA | 3 | 94,581 | 0.99 (0.90,1.09) | 0.868 | 0 | 0 | 0.395 | |
| **Dose of clopidogrel** | | | | | | | | |
| 75 mg QD | 9 | 34,267 | 0.72 (0.62,0.83) | <0.001 | 30.8 | 0.013 | 0.172 | <0.001 |
| 600 mg and 75 mg BID | 1 | 400 | 0.36 (0.13,0.98) | 0.046 | – | – | – | |
| 300 mg and 75 mg QD | 4 | 8764 | 0.82 (0.51,1.31) | 0.408 | 93.3 | 0.197 | <0.001 | |
| NA | 3 | 94,581 | 0.99 (0.90,1.09) | 0.868 | 0 | 0 | 0.394 | |
| **All-cause death** | | | | | | | | |
| **Region** | | | | | | | | |
| Europe | 3 | 13,286 | 0.87 (0.66,1.14) | 0.319 | 44.8 | 0.028 | 0.164 | 0.104 |
| North America | 2 | 73,765 | 1.03 (0.86,1.24) | 0.743 | 19.7 | 0.004 | 0.264 | |
| Asia | 9 | 46,793 | 0.73 (0.59,0.89) | 0.002 | 12.0 | 0.012 | 0.335 | |
| Oceania | 1 | 4949 | 0.92 (0.70,1.21) | 0.550 | – | – | – | |
| South America | 1 | 1676 | 0.65 (0.38,1.11) | 0.115 | – | – | – | |
| **Study design** | | | | | | | | |
| RCT | 3 | 13,294 | 0.87 (0.74,1.01) | 0.076 | 0 | 0 | 0.478 | 0.776 |
| Non-RCT | 13 | 127,175 | 0.84 (0.70,1.00) | 0.049 | 48.7 | 0.043 | 0.025 | |
| **Single-center/multicenter** | | | | | | | | |
| Single-center | 4 | 4905 | 1.12 (0.78,1.61) | 0.534 | 0 | 0 | 0.774 | 0.130 |
| Multicenter | 12 | 135,564 | 0.83 (0.72,0.96) | 0.012 | 49.1 | 0.028 | 0.028 | |
| **Follow-up duration** | | | | | | | | |
| ≤6 months | 1 | 2714 | 0.92 (0.53,1.57) | 0.748 | – | – | – | 0.795 |
| >6 months | 13 | 137,755 | 0.85 (0.74,0.98) | 0.023 | 43.6 | 0.027 | 0.036 | |
| **Dose of ticagrelor** | | | | | | | | |
| 180 mg and 90 mg BID | 5 | 32,437 | 0.90 (0.65,1.17) | 0.429 | 45.3 | 0.039 | 0.120 | 0.018 |
| 90 mg BID | 9 | 34,267 | 0.74 (0.65,0.85) | <0.001 | 0 | 0 | 0.514 | |
| NA | 2 | 73,765 | 1.03 (0.86,1.24) | 0.743 | 19.7 | 0.004 | 0.264 | |
| **Dose of clopidogrel** | | | | | | | | |
| 75 mg QD | 9 | 34,267 | 0.74 (0.65,0.85) | <0.001 | 0 | 0 | 0.514 | 0.080 |
| 600 mg and 75 BID | 1 | 3703 | 1.17 (0.79,1.75) | 0.427 | – | – | – | |
| 300 mg and 75 mg QD | 3 | 8464 | 0.94 (0.74,1.20) | 0.629 | 0 | 0 | 0.694 | |
| NA | 3 | 94,035 | 0.90 (0.65,1.25) | 0.535 | 75.3 | 0.062 | 0.017 | |
| **Major bleeding** | | | | | | | | |
| **Region** | | | | | | | | |
| Europe | 2 | 9583 | 1.07 (0.81,1.41) | 0.640 | 41.4 | 0.021 | 0.191 | 0.023 |
| North America | 2 | 11,795 | 1.51 (1.29,1.77) | <0.001 | 0.0 | 0 | 0.936 | |
| Asia | 3 | 12,793 | 1.27 (0.98,1.65) | 0.067 | 0.0 | 0 | 0.502 | |
| Oceania | 1 | 4949 | 0.97 (0.77,1.22) | 0.795 | – | – | – | |
| South America | 1 | 1676 | 1.35 (0.86,2.12) | 0.195 | – | – | – | |
| **Study design** | | | | | | | | |
| RCT | 3 | 13,294 | 1.03 (0.86,1.22) | 0.769 | 34.3 | 0.009 | 0.218 | 0.004 |
| Non-RCT | 6 | 27,502 | 1.42 (1.25,1.61) | <0.001 | 0 | 0 | 0.759 | |
| **Single-center/multicenter** | | | | | | | | |
| Single-center | 1 | 480 | 0.71 (0.19,2.68) | 0.615 | – | – | – | 0.426 |
| Multicenter | 8 | 40,316 | 1.23 (1.03,1.46) | 0.022 | 63.3 | 0.034 | 0.008 | |
| **Dose of ticagrelor** | | | | | | | | |
| 180 mg and 90 mg BID | 2 | 11,185 | 1.51 (1.29,1,77) | <0.001 | 63.7 | 0.068 | 0.097 | 0.005 |
| 90 mg BID | 6 | 23,861 | 1.08 (0.95,1.22) | 0.257 | 0 | 0 | 0.441 | |
| NA | 1 | 5750 | 1.16 (0.75,1.80) | 0.514 | – | – | – | |

(*continued on next page*)

**Table 2** (*continued*)

| Subgroup | No. of studies | No. of patients | Effect value | | Heterogeneity | | | P $_{interaction}$ |
|---|---|---|---|---|---|---|---|---|
| | | | HR (95%CI) | *P*-value | *I* [2]% | Tau [2] | *P*-value | |
| **Dose of clopidogrel** | | | | | | | | |
| 75 mg QD | 6 | 23,861 | 1.08 (0.95,1.22) | 0.257 | 0 | 0 | 0.441 | 0.005 |
| 300 mg and 75 mg QD | 2 | 11,185 | 1.51 (1.29,1,77) | <0.001 | 63.7 | 0.068 | 0.097 | |
| NA | 1 | 5750 | 1.16 (0.75,1.80) | 0.514 | – | – | – | |
| **All bleeding** | | | | | | | | |
| **Region** | | | | | | | | |
| Europe | 2 | 9583 | 1.45 (0.94,2.25) | 0.093 | 92.5 | 0.092 | <0.001 | <0.001 |
| North America | 3 | 74,375 | 1.43 (1.30,1.57) | <0.001 | 0.0 | 0 | 0.498 | |
| Asia | 6 | 54,279 | 1.40 (1.04,1.89) | 0.026 | 67.3 | 0.080 | 0.009 | |
| Oceania | 1 | 4949 | 1.05 (0.86,1.28) | 0.624 | – | – | – | |
| South America | 1 | 1676 | 1.81 (1.56,2.11) | <0.001 | 0 | – | – | |
| **Study design** | | | | | | | | |
| RCT | 3 | 13,294 | 1.23 (0.98,1.56) | 0.079 | 68.2 | 0.028 | 0.043 | 0.168 |
| Non-RCT | 10 | 131,568 | 1.49 (1.29,1.72) | <0.001 | 71.9 | 0.028 | <0.001 | |
| **Single-center/multicenter** | | | | | | | | |
| Single-center | 3 | 21,696 | 1.87 (1.34,2.60) | <0.001 | 0 | 0 | 0.719 | 0.090 |
| Multicenter | 10 | 123,166 | 1.37 (1.19,1.58) | <0.001 | 81.1 | 0.037 | <0.001 | |
| **Follow-up duration** | | | | | | | | |
| ≤6 months | 1 | 400 | 1.43 (0.56,3.62) | 0.453 | – | – | – | 0.986 |
| >6 months | 12 | 144,462 | 1.42 (1.24,1.62) | <0.001 | 78.4 | 0.037 | <0.001 | |
| **Dose of ticagrelor** | | | | | | | | |
| 180 mg and 90 mg BID | 4 | 26,420 | 1.12 (0.75,1.68) | 0.574 | 74.2 | 0.112 | 0.009 | 0.422 |
| 90 mg BID | 6 | 23,861 | 1.51 (1.25,1.85) | <0.001 | 80.3 | 0.042 | <0.001 | |
| NA | 3 | 94,581 | 1.45 (1.24,1.66) | <0.001 | 37.1 | 0.005 | 0.204 | |
| **Dose of clopidogrel** | | | | | | | | |
| 75 mg QD | 6 | 23,861 | 1.52 (1.25,1.85) | <0.001 | 80.3 | 0.042 | <0.001 | 0.846 |
| 600 mg and 75 BID | 1 | 400 | 1.43 (0.56,3.62) | 0.453 | – | – | – | |
| 300 mg and 75 mg QD | 2 | 5750 | 1.32 (0.81,2.13) | 0.262 | 84.0 | 0.102 | 0.012 | |
| NA | 4 | 114,851 | 1.33 (1.04,1.70) | 0.024 | 75.5 | 0.037 | 0.007 | |

NO., number of; HRs, hazard ratio; CI, confidence interval; NA, not available; RCT, randomized controlled trials, BID, bis in die; QD, quaque die.

efficacy endpoint of major adverse cardiovascular events (MACEs) compared to clopidogrel (HR 0.74; 95% CI, 0.62, 0.89, $P = 0.001$; $I^2 = 88.3\%$, $P < 0.001$; Fig. 2). The finding was consistently observed in most of the subgroup analyses, whether the study is single-center/multicenter, region, the follow-up duration, study design may be the source of heterogeneity (Table 2). There was a lower risk of MACE with ticagrelor compared with clopidogrel in Europe (HR 0.86, 95% CI, 0.75, 0.98; $P = 0.028$; $I^2 = 0.0\%$, $P = 0.587$) and Asia (HR 0.64, 95% CI, 0.52, 0.79; $P < 0.001$; $I^2 = 66.5\%$, $P = 0.00$) but not North America (HR 1.00, 95% CI, 0.91, 1.11, $P = 0.958$; $I^2 = 0.0\%$, $P = 0.436$), Oceania (HR 0.91, 95% CI, 0.74, 1.11, $P = 0.357$), and South America (HR 1.81, 95% CI, 1.56, 2.11, $P < 0.001$) (Supplementary Appendices 7). Similarly, there was a lower risk of MACEs with ticagrelor compared with clopidogrel in the subgroup of multicenter (HR 0.87, 95% CI, 0.79, 0.97, $P = 0.012$; $I^2 = 48.4\%$, $P = 0.036$) and single-center (HR 0.50, 95% CI, 0.46, 0.55, $P < 0.001$; $I^2 = 0$, P = 0.629) (Supplementary Appendices 8). And there was a lower risk of MACEs with ticagrelor compared with clopidogrel in the subgroup of follow-up duration ≤6 months (HR 0.55, 95% CI, 0.46, 0.77, $P < 0.001$; $I^2 = 49.5\%$, $P = 0.138$) and follow-up duration > 6 months (HR 0.82, 95% CI, 0.73, 0.93, $P = 0.001$; $I^2 = 58.7\%$, P = 0.003) (Supplementary Appendices 12).

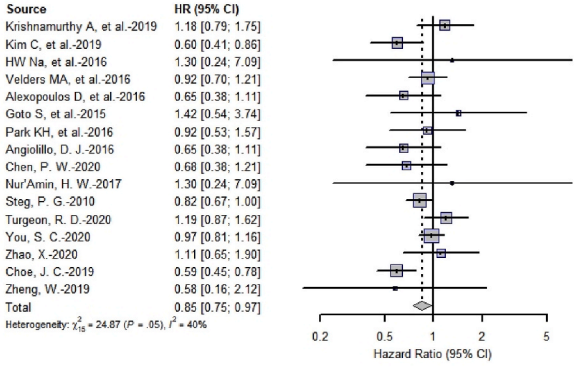


**Fig. 3.** Forest plot of all-cause mortality.

### 4.2. All-cause mortality

A total of 140,469 patients were identified in 16 studies. The all-cause mortality was reduced by ticagrelor (HR 0.85; 95% CI, 0.75, 0.97, $P = 0.019$; $I^2 = 39.7\%$, $P = 0.052$; Fig. 3).There was a lower risk related to all-cause mortality when comparing ticagrelor to clopidogrel in Asia (HR 0.73, 95% CI, 0.59, 0.89, $P = 0.002$; $I^2 = 12.0\%$, $P = 0.335$)not but Europe (HR 0.87, 95% CI, 0.66, 1.14, $P = 0.319$; $I^2 = 44.8\%$, $P = 0.164$), North America (HR 1.03, 95% CI, 0.86, 1.24, $P = 0.743$; $I^2 = 19.7\%$, $P = 0.264$), Oceania (HR 0.92, 95% CI, 0.70, 1.21, $P = 0.550$), and South America (HR 0.65, 95% CI, 0.38, 1.11, $P = 0.115$) (Supplementary Appendices 13). Similarly, there was a lower risk of all-cause mortality when comparing ticagrelor to clopidogrel in the subgroup of multicenter (HR 0.83, 95% CI, 0.72, 0.96, $P = 0.012$; $I^2 = 49.1\%$, $P = 0.028$) but not single-center (HR 1.12, 95% CI, 0.78, 1.61, $P = 0.534$; $I^2 = 0$, $P = 0.774$) (Supplementary Appendices 14). And there was a lower risk of all-cause mortality with ticagrelor compared with clopidogrel in the subgroup of follow-up duration > 6months (HR 0.85, 95% CI, 0.74, 0.98, $P = 0.023$; $I^2 = 43.6\%$, $P = 0.036$) but not follow-up duration ≤6months (HR 0.92, 95% CI, 0.53, 1.57, $P = 0.748$) (Supplementary Appendices 18). Finally, the subgroup analysis showed that region, study design, single-center or multicenter, follow-up duration, dose of clopidogrel and dose of ticagrelor were all not the sources of heterogeneity (Supplementary Appendices 13-18**)**.

### 4.3. Stroke

In this meta-analysis of 10 studies involving 123,442 patients, there was no significant difference in the occurrence of stroke between the ticagrelor and clopidogrel groups. (HR 1.02,95% CI, 0.74, 1.41, $P = 0.887$; $I^2 = 64.9\%$, $P = 0.002$) (Supplementary Appendices 19).

### 4.4. MI

A total of 117,162 patients were identified in 13 studies. No significant difference was seen in MI between ticagrelor and clopidogrel groups (HR 0.90, 95% CI, 0.78, 1.05, $P = 0.172$; $I^2 = 57.6\%$, $P = 0.005$) (Supplementary Appendices 20).

### 4.5. Urgent revascularization

A total of 80,916 subjects were identified in 7 studies. No significant difference was seen in urgent revascularization between ticagrelor and clopidogrel groups (HR 0.90, 95% CI, 0.74, 1.09, $P = 0.275$; $I^2 = 23.8\%$, $P = 0.247$) (Supplementary Appendices 21).

## 5. Safety

### 5.1. Major bleeding

A total of 12,793 patients were identified in 9 studies. The primary safety endpoint of major bleeding with ticagrelor compared with clopidogrel was HR 1.21 (95% CI, 1.02, 1.44, $P = 0.026$, $I^2 = 59.3\%$, $P = 0.012$; Fig. 4). The finding was consistently observed in most of the subgroup analyses, study design and region may be the source of heterogeneity (Table 2). Major bleeding had no significant difference in Europe (HR 1.07, 95% CI, 0.81, 1.41, $P = 0.640$; $I^2 = 41.4\%$, $P = 0.191$), North America (HR 1.51, 95% CI, 1.29, 1.77, $P < 0.001$; $I^2 = 0$, $P = 0.936$), Oceania (HR 0.97, 95% CI, 0.77, 1.22, $P = 0.795$), South America (HR 1.35, 95% CI, 0.86, 2.12, $P = 0.195$) and Asia (HR 1.27, 95% CI, 0.98, 1.65, $P = 0.067$; $I^2 = 0$, $P = 0.502$) (Supplementary Appendices 22). In major bleeding, there was a higher risk with ticagrelor compared with clopidogrel in the subgroup of non-RCT studies (HR 1.42, 95% CI, 1.25, 1.61, $P < 0.001$; $I^2 = 0$, $P = 0.759$; $I^2 = 34.3\%$, $P = 0.218$) but not RCT studies (HR 1.03, 95% CI, 0.86, 1.22, $P = 0.769$; $I^2 = 59.3\%$, $P = 0.012$) (Supplementary Appendices 24). However, the subgroup analysis showed that whether the study is single center or multicenter was not sources of heterogeneity (Supplementary Appendices 23**)**.

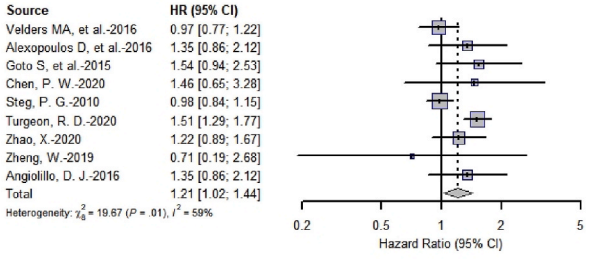


**Fig. 4.** Forest plot of major bleeding.

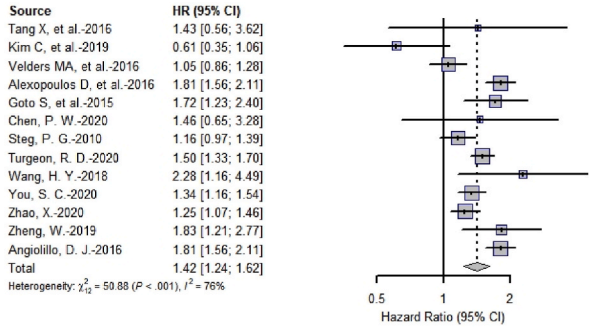


**Fig. 5.** Forest plot of all bleeding.

**Table 3**
Meta-regressions.

| Factors | Coefficient | 95% CI | *P*-value |
|---|---|---|---|
| Male sex ratio | −0.005 | (−0.029, 0.019) | 0.671 |
| Age | 0.024 | (−0.013, 0.061) | 0.187 |
| Follow-up time | 0.031 | (−0.085, 0.146) | 0.584 |
| Study design (RCT) | | | |
| Non-RCT | −0.345 | (−0.743, 0.052) | 0.084 |
| Region (Asia) | Ref | | |
| Europe | 0.385 | (0.013, 0.757) | 0.043 |
| North America | 0.488 | (0.111, 0.864) | 0.015 |
| Oceania | 0.385 | (−0.138, 0.908) | 0.136 |
| South America | 0.231 | (−0.404, 0.865) | 0.448 |
| Single-center/multicenter (single-center) | Ref | | |
| Multicenter | −0.332 | (−0.663, −0.001) | 0.049 |
| Dose of clopidogrel (300 mg and 75 mg QD) | Ref | | |
| 600 mg and 75 QD | 0.081 | (−0.678, 0.839) | 0.823 |
| 75 mg QD | −0.159 | (−0.609, 0.291) | 0.464 |
| NA | 0.022 | (−0.495, 0.540) | 0.929 |
| Dose of ticagrelor (180 mg and 90 mg BID) | Ref | | |
| 90 mg BID of ticagrelor | −0.086 | (−0.454, 0.281) | 0.625 |
| NA | 0.243 | (−0.216, 0.701) | 0.278 |

NA: not available.

### 5.2. All bleeding

A total of 144,862 subjects were identified in 13 studies. The primary safety endpoint of all bleeding with ticagrelor compared with clopidogrel was HR 1.42 (95% CI, 1.24, 1.62; $P < 0.001$, $I^2 = 76.4\%$, $P < 0.001$; Fig. 5). The finding was consistently observed in most of the subgroup analyses, region may be the source of heterogeneity (Table 2). There was a higher risk of all bleeding with ticagrelor compared with clopidogrel in North America (HR 1.43, 95% CI, 1.30, 1.57, $P < 0.001$; $I^2 = 0$, $P = 0.498$), South America (HR 1.81, 95% CI, 1.56, 2.11, $P < 0.001$), and Asia (HR 1.40, 95% CI, 1.04, 1.89, $P = 0.026$; $I^2 = 67.3$, $P = 0.009$) not but Europe (HR 1.45, 95% CI, 0.94, 2.25, $P = 0.093$; $I^2 = 92.5\%$, $P < 0.001$) and Oceania (HR 1.05, 95% CI, 0.86, 1.28, $P = 0.624$) (Supplementary Appendices 27). However, the subgroup analysis showed that whether the study is single center or multicenter, study design, follow-up duration, dose of clopidogrel and dose of ticagrelor were not sources of heterogeneity (Supplementary Appendices 28-32).

### 5.3. Sensitivity analysis and publication bias

Through meta-regression analysis, it was found that the source of heterogeneity in the results of the studies may be attributed to factors such as whether the study was conducted in a single-center or multicenter, as well as the geographical region in which the study was conducted (Table 3). To assess the impact of individual studies on the overall results of our meta-analysis, we conducted a sensitivity analysis by sequentially excluding each eligible study. The results, as depicted in Supplementary Appendices 33-39, revealed that the exclusion of any single study did not significantly alter the pooled hazard ratios (HRs), indicating the robustness and stability of our findings. In addition, no significant asymmetry was apparent by visual inspection of the funnel plot of studies reporting on MACEs (Supplementary Appendices 40). Egger's test did not show significant publication bias ($P = 0.64$).

## 6. Discussion

Our systematic review and meta-analysis comprehensively investigated the efficacy and safety between ticagrelor and clopidogrel

in ACS patients who underwent PCI, and explored the potential source of heterogeneity through subgroup analyses based on geographical region, dosage, single-center versus multicenter studies, and the duration of follow-up. Our findings suggested that ticagrelor was more effective than clopidogrel in reducing the risk of MACEs and all-cause mortality in ACS patients undergoing PCI. However, ticagrelor was associated with an increased risk of bleeding events, including all bleeding and major bleeding. No significant differences were observed between ticagrelor and clopidogrel groups in terms of MI, stroke, and urgent revascularization. Additionally, our subgroup analyses indicated that geographical region, study design, follow-up duration, single-center/multicenter status, and the dosage of ticagrelor and clopidogrel were potential sources of heterogeneity. Specifically, ticagrelor exhibited greater effectiveness in Asian and European populations, whereas its efficacy was less prominent in American and Oceania populations.

The difference in efficacy between ticagrelor and clopidogrel may be attributed to their distinct mechanisms of action. Clopidogrel exerts long-term antiplatelet effects by binding irreversibly to the P2Y12 receptor, which is an ADP receptor located on the platelet membrane. In contrast, ticagrelor binds reversibly to the P2Y12 receptor, blocking ADP-induced platelet activation in a noncompetitive manner [30,42]. Therefore, ticagrelor exhibits a faster onset of action compared to clopidogrel as it does not rely on liver-mediated activation through cytochrome P450 2C19(CYP2C19).

Numerous studies have reported adverse clinical outcomes associated with the use of different medications in patients with ACS undergoing PCI. For instance, despite the widespread use of dual antiplatelet therapy (DAPT) consisting of aspirin and clopidogrel in routine practice, there remains a significant risk of primary adverse clinical outcomes. Ongoing research is assessing the efficacy of new potent P2Y12-receptor antagonists, such as ticagrelor or prasugrel. Based on a nationwide, prospective, multicenter online registry trial [19] and a retrospective cohort study [32], the ticagrelor in ACS patients undergoing PCI reduced the MACE incidence. In contrast, a retrospective cohort study involving 31,290 ACS patients compared the risk of MACEs at 12 months between those treated with ticagrelor (3484 patients) and clopidogrel (23,116 patients). The study revealed no significant difference in the risk of MACE between the two treatment [30]. In addition, a recent meta-analysis found no reduction in MACE and all-cause mortality with ticagrelor after PCI, but instead increased the risk of bleeding [43]. Another meta-analysis showed that ticagrelor is more beneficial and safer among Europeans and Americans than clopidogrel [14], but there is an increased risk of bleeding among Asians. Therefore, antiplatelet drugs should be chosen carefully. Still, ticagrelor's efficacy and clinical safety outcomes are uncertain; thus, they should be discussed further due to the variation in the different subgroups.

The present results of the studies showed ticagrelor reduced the risk of MACEs between Europeans and Asians compared with clopidogrel. This could be due to the different mechanisms of action between the two drugs. The difference in effectiveness between Ticagrelor and Clopidogrel in treating ACS patients undergoing PCI is likely attributed to their distinct pharmacokinetics and the conversion process of Clopidogrel to its active form. Specifically, ticagrelor is a direct agent of the ADP receptor which could inhibit platelet aggregation, thus superior to clopidogrel. Ticagrelor increases the risk of all bleedings compared with clopidogrel because ticagrelor has a more powerful inhibition effect of platelet aggregation [15,24,44].

The previous meta-analysis did not examine the importance of ticagrelor's maintained or loading dosage [13]. In this study, we made the subgroup of doses in drugs. Though it is not statistically significant, it may be a key influence factor on the clinical outcome because ticagrelor is dose-dependent and reversible [45]. Moreover, those articles [10,21,30,46] reported adverse drug events, including dyspnea, bradycardia, ventricular tachycardia, ventricular extrasystoles, epigastric pain, and any uric acid adverse event. The adverse drug events cannot be combined due to the absence of effect size data. However, the adverse drug events cannot be combined due to the lack of the effect size data. Ticagrelor, a new P2Y12 receptor antagonist, has unclear drug mechanisms and poses a higher risk of adverse drug events compared with clopidogrel. Our meta-analysis has several other outcomes, including the ADP inhibition rate, inflammatory biomarkers, and vascular endothelial function [20,21,23]. The effect of the two drugs on these outcomes is unclear, so further mechanism research is needed.

Our meta-analysis has some limitations. Firstly, we couldn't make a meta-analysis of adverse drug events because of a lack of relevant data. Secondly, the original research identified discrepancies in the definition of bleeding, potentially contributing to heterogeneity. However, further discussion could not be carried out due to the limitation of the original data. Thirdly, the absence of PCI procedures data, including the time of the procedure and types of implanted stents, would prevent us from merging data and exploring the influence of these factors on the results. Fourthly, an estimated high degree of heterogeneity among studies was found. However, the more conservative random-effects model and our additional analyses, including subgroup analysis and sensitivity analysis with the exclusion of one trial at a time were used to overcome this limitation partly. Therefore, the results of this study needed to be interpreted with caution due to the influence of heterogeneity. Fifthly, the quality of the original study was uneven, and observational studies have influenced the included studies. Lastly, the limited number of RCTs included in our study and the small sample size compared to non-RCTs may contribute to the heterogeneity observed. Therefore, future research should focus on conducting multi-center and large-sample RCT studies to enhance the reliability of meta-analysis results.

## 7. Conclusions

Ticagrelor has demonstrated superior efficacy compared to clopidogrel in ACS patients undergoing PCI, particularly in Asia and Europe. Nevertheless, it is crucial to acknowledge that the utilization of ticagrelor is linked to a heightened risk of bleeding. To provide guidance for clinical decision-making regarding the use of ticagrelor, future multicenter randomized trials that are relevant and encompass longer follow-up periods are necessary.

## Financial disclosures

None.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## CRediT authorship contribution statement

**Jing Yang:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Rui Zhang:** Writing – review & editing. **Qianqian Liu:** Writing – review & editing, Writing – original draft. **Yuping Bai:** Formal analysis, Data curation. **Liyan Zhang:** Formal analysis. **Tingting He:** Formal analysis. **Ziru Zhao:** Methodology. **Min Huang:** Data curation. **Yunshan Cao:** Funding acquisition, Formal analysis. **Xiaopeng Wang:** Writing – review & editing. **Min Zhang:** Resources, Project administration, Methodology, Investigation, Funding acquisition.

## Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Min Zhang reports article publishing charges was provided by Basic Research Innovation Group Project of Gansu Province. Min Zhang reports administrative support was provided by the National Natural Science Foundation of China. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Abbreviations

| | |
|---|---|
| ACS | Acute coronary syndrome |
| PCI | Percutaneous coronary intervention |
| AMI | Acute myocardial infarction |
| MACE | Major adverse cardiovascular event |
| MI | Myocardial infarction |
| RCTs | Randomized controlled trials |
| DES | Drug-eluting stents |

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e26553.

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